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09/778,154	02/05/2001	Seo Hong Yoo	APAP31191-A 072852.0117	5489

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EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 12/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/778,154	YOO, SEO HONG	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *138-148* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *138-148* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 138-148 are pending and examined.

Withdrawn Rejections and Objections

2. The rejection of claim 146 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, because the claim formerly stated "an agent having prolonging survival time", is withdrawn in view of applicant's amendment to claim 148, entered 8/2/2005.

3. The objections to the specification for new matter is withdrawn in regards to the amendments to the specification at p. 56, lines 1-9, p. 57, lines 1-9, p. 58, lines 1-5, p. 60, lines 1-9, are withdrawn in view of applicant's amendments, entered 8/2/2005, which restore the original language of the specification as filed.

Election/Restrictions

4. Applicant's election, filed 9/23/2002, of Group VI, original claims 138-147, and the species of ursodeoxycholic acid (Species Group I) and a starch conversion product (Species Group II) is again acknowledged and maintained.

Priority

5. The instant application is a continuation-in-part of Serial No. 09/357,549, filed 7/20/1999, now US Patent 6,251,428, which claims benefit of 60/094,069, filed 7/24/1998; and claims benefit of US Provisional Application No. 60/180,268, filed 2/4/2000.

Response to Yoo Declaration II

6. The second declaration of Seo Hong Yoo (hereinafter "Yoo Declaration II") entered 8/2/2005 under 37 CFR 1.132, has been considered but is ineffective to overcome the reference of Japanese Patent No. JP62153220, to Nakazawa et al.

It is noted that the Yoo Declaration II is similar to the earlier entered declaration of Seo Hong Yoo, entered 5/17/2004 (hereinafter Yoo Declaration I). Both Yoo Declaration I and Yoo Declaration II report comparisons between the compositions taught in the instant application with the compositions of the reference of Nakazawa.

Yoo Declaration II now provides spectrophotometric measurements, as well as visual assessments, of the turbidity of applicant's solutions. However, Yoo Declaration II, as in Yoo Declaration I, provides only visual assessments, and not spectrophotometric measurements, of the turbidity of solutions that the Declarant states were prepared according to the methods of Nakazawa et al. See Yoo Declaration II at para 7-9. Declarant provides the publication of Dasta, J.F. et al., to show that visual inspection is an art recognized means of clarity evaluation. Declarant states that one of

ordinary skill in the art would have recognized that "clear" means substantially free of precipitate or particles.

The Yoo Declaration II has been considered, but is not effective for overcoming the reference of Nakazawa et al. The claimed invention is drawn to a product, i.e., a clear aqueous solution. The Yoo Declaration II considers the quality of being clear as a physical property not shared by solutions prepared according to the prior art method of Nakazawa et al. However, the Yoo Declarations I and II do not provide spectrophotometric measurements of the physical property of clarity, or turbidity, of the solutions produced by the alleged methods of Nakazawa et al., even though visual assessments for those solutions were provided. The Yoo Declaration II provides the publication of Dasta, J.F. et al. to indicate that subjective, visual categorization of clearness is even "more sensitive than turbidimetric methods in some cases", (Yoo Declaration II at para 9, citing Dasta J.F., et al., at p. 2363, right column). However, the Yoo Declaration II at Table 4, no longer ascribes the property of being "mostly clear with some undissolved matter", as in the Yoo Declaration I, at pp. 4-5, bridging paragraph, to the compositions of Nakazawa et al. Declarant does not address why the visual assessments of the solutions of Nakazawa et al. have changed. This seeming inconsistency in the visual assessments among the Yoo Declarations, (notwithstanding Declarant's conclusion at para 8 of the Yoo II, that the results of the two Yoo Declarations are "wholly consistent"), would seem to question the applicability of visual assessment and the teachings of Dasta, to the present circumstances.

In the Yoo Declaration I, Declarant stated that solutions according to Nakazawa et al. became "mostly clear with some undissolved matter", (Yoo Declaration I at pp. 4-5, bridging paragraph). See Office action, mailed 2/3/2005. It appears now that the Declarant no longer finds these solutions "mostly clear" and that "one of ordinary skill in the art would have recognized, based in part on the instant specification and Dasta et al., that 'clear' means substantially free of precipitate or particles." Yoo Declaration II at para 10. The examiner disagrees that the quality of being clear means that a solution must be free of precipitates or particles, if that means that a solution cannot be in contact with precipitates. The examiner respectfully submits that a solution in a container, for example, might be clear, even though the container may have precipitate that had settled to the bottom of that container. Solutes and precipitates may be in equilibrium in such a container.

Declarant does not indicate how the methods used to make the claimed invention differ from the methods taught by Nakazawa et al. Declarant measures the solutions within a period of two days, but the claims as drawn, are silent as to any duration. The product claims to the solution comprise no limitation as to precipitates or particles.

Therefore, examiner respectfully submits that the Yoo Declaration II does not overcome the prior art reference of Nakazawa et al., when compared to the claimed invention.

Objections to the Specification

7. The amendment filed 7/3/2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. This objective is maintained for the reasons of record as set forth in the previous Office actions. The added material which is not supported by the original disclosure is as follows:

There is no support in the specification as filed for "aqueous soluble ~~sulfate~~ bismuth chelate" at p. 53, lines 1-5 (Example VIII).

There is no support in the specification as filed for "Bismuth ~~citrate~~ sulfate 5 g" at p. 53, lines 6-14.

There is no support in the specification as filed for "Bismuth ~~citrate~~ sulfate 5 g" at p. 53, line 19.

There is no support in the specification as filed for "Bismuth ~~citrate~~ sulfate 4 g" at p. 54, line 10.

There is no support in the specification as filed for "Bismuth ~~citrate~~ sulfate 4 g" at p. 55, lines 1-10.

Applicant argues that the formulations found in the Examples of the specification as filed include bismuth sulfate in an indicated amount. This is not found persuasive, because in the formulation found in the specification as filed, bismuth *citrate*, and not bismuth sulfate, is disclosed with indicated amounts.

Applicant argues that the language "aqueous soluble" is fully supported, because the application as originally filed "is replete with disclosures of aqueous solutions comprising dissolved bismuth including the very Example where this phrase is to be inserted", (Reply at p. 11). This is not found persuasive, because the specification as filed, particularly at the location pointed to by applicant, does not provide support for a limitation drawn to aqueous soluble bismuth *chelate*.

8. The amendment filed **8/2/2005** is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicant must point, with particularity, as to where support may be found in the specification as filed, for the amendment changing "DMT" to –dacarbazine–. This objection to the specification is necessitated by applicant's amendments to the specification, entered 8/2/2005.

9. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. Claims 145-147 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for new matter. This rejection maintains the reasons of record as set forth in the previous Office action. This rejection is repeated below for the convenience of the reader.

Claims 145-147, added by amendment filed 1/8/2002, state the limitations "anticonvulsant activity", "an agent having prolonging survival time in hypoxic conditions", and "the group consisting of stomatitis, gingivoglossitis and toothache", respectively. There does not appear to be support for these limitations to the claims in the specification as filed. Applicant must point, with particularity, to where in the specification as filed, support for these limitations may be found.

Applicant argues a number of compounds "with each of the recited properties have been provided in the specification as originally filed", (Reply at pp. 11-12). Applicant states: "Examples of agents with anticonvulsant activity include any of the disclosed anti-asthma compounds disclosed such as albuterol sulfate, (Reply at p. 12)." Applicant argues that the property of prolonging survival under hypoxic conditions is supported by disclosure of specific drugs, such as hydrazine, isoxsuprine, nylidrin, dyphylline, pirbuterol, colfosceril palmitate, which applicant states are vasodilators or bronchodilators. Applicant argues that agents for alleviating or ameliorating stomatitis, gingivolglossitis and toothache, "include any of the antiviral compounds disclosed, particularly those with anti-hepatitis activity (e.g., acyclovir, interferon, penciclovir)", (Reply at p. 12).

Response to Arguments

Applicant's arguments entered 8/2/2005 have been fully considered but they are not persuasive.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145. Applicant's representative provides no objective evidence that the practitioner would envision the added limitations of the amended claim upon the disclosure of lists of specific drugs, as in the specification at p. 25, line 13 to p. 27, line 9. Applicant's representative does not provide objective evidence that albuterol is an anti-asthma drug, or evidence that albuterol should therefore be recognized as an anticonvulsive drug. Applicant's representative does not provide objective evidence that the claimed survival under hypoxic conditions is supported by the specific drugs listed, i.e., hydrazine, isoxsuprine, nylidrin, dyphylline, pirbuterol, or colfosceril palmitate, and does not provide objective evidence that these drugs are vasodilators or bronchodilators. Applicant does not provide evidence that antiviral compounds, particularly anti-hepatitis compounds, would lead one of skill in the art to envision agents for stomatitis, gingivolglossitis and toothache. Therefore, the specification as filed does not provide support for the amendments to claims 145-147, entered 1/8/2002. It appears that nowhere in the specification as filed, is there support for claim limitations to anti-convulsive agents, drugs to treat hypoxia, stomatitis, gingivolglossitis or toothache.

Claim Rejections - 35 USC § 112, Second Paragraph

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

11. Claims 138-148 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection maintains the reasons of record as set forth in the previous Office action. The rejections are copied below for the convenience of the reader.

The term "clear" in claims 138, its dependent claims, and 148, is a relative term that renders the claim indefinite. The term "clear" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of clearness or transparency or clarity, and one of skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Claims 138, its dependent claims and 148, recite the language "within a selected range of pH values", which renders the claims vague and indefinite, because the selecting the range of pH values would read on a mental step and does not define the range of the relevant physical property, so that one of skill in the art would not be reasonably apprised of the metes and bounds of the claimed composition.

Applicant argues that the specification at p. 19, lines 9-10, set forth the metes and bounds of the term "clear", as used in the claims, and states:

> These aqueous solution systems of bile acid are substantially free of precipitate or particles. A further advantage of this invention is that the aqueous solution systems demonstrate no changes in physical appearance such as changes in clarity, color or odor following the addition of strong acids or alkali even after several months observation under accelerated conditions of storage at 50.degree. C.

Specification at p. 19, lines 9-14.

Response to Arguments

Applicant's arguments entered 8/2/2005 have been fully considered but they are not persuasive.

The specification as filed does not provide a limiting definition for the term "clear". The examiner respectfully submits that the term "clear" is not defined to mean "substantially free of precipitate or particles". Indeed, a clear solution may contain settled precipitate. Furthermore, these limitations are not found in the claims. The passage to which the applicant points, does not recite the term "clear", at all. Therefore, the term "clear" is considered to be a relative term, as the specification does not reasonably apprise one of skill in the arts as to the metes and bounds of the claimed invention.

Applicant has not traversed the rejection of claim 138, for stating "within a selected range of pH values", as reading on a mental step. It is noted that the claims are drawn to products, but the aforementioned limitation is too vague and indefinite to provide the metes and bounds of the structure of the claimed solution. Therefore, the rejection of claim 138 is maintained over the instant ground.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

12. Claims 138-141 are rejected under 35 U.S.C. 102(b) as being anticipated by Japan Publication No. 62153220, Formal Translation, (IDS filed 5/17/2004) to Shinzo Nakazawa and Satoshi Hisano (English translation of "Nakazawa et al."; also called "Satoshi" by the applicant and in the Yoo Declaration I). It is noted that the Formal Translation of Japan Publication No. 62153220 was the addendum to the Affidavit or

Exhibits, filed 5/17/2004. This rejection maintains the reasons of record as set forth in the previous Office action. This rejection is copied below for the convenience of the reader.

Claims 138-141 are drawn to a clear aqueous solution comprising; (i) a first material selected from the group consisting of an aqueous soluble bile acid salt, a bile acid conjugated with an amine by an amide linkage that is ursodeoxycholic acid (elected species), and combinations thereof; (ii) an aqueous soluble starch conversion product (elected species); and (iii) water, wherein the first and second materials both remain in solution for all pH values of the solution within a selected range of pH values.

Japan Publication No. 62153220, Formal Translation, (IDS filed 5/17/2004) throughout the publication and especially at p 2, teach a clear liquid agent (p. 2, para 2, claim 1 and para 3; which reads on a clear aqueous solution) comprising ursodeoxycholic acid or chenodeoxycholic acid (p. 2, para 2, claim 2) and a dextrin starch derivative that is maltodextrin, amylodextrin or erythrodextrin, (p. 2, claim 2, reading on an aqueous soluble starch conversion product (elected species)); and (iii) water (p. 2, claim 1), wherein the first and second materials both remain in solution for all pH values of the solution within a selected range of pH values (p. 9, para 16).

The Yoo Declaration is ineffective to overcome Nakazawa et al. as a reference for the reasons provided above in paragraphs 9 of the instant Office action. Briefly, the Yoo Declaration states that solutions prepared by the method of Nakazawa et al., provide solutions that do not remain clear for as long a duration (*e.g.*, after 5 months) as those of the instant application. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., long-term clearness) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, the examiner respectfully submits that the Yoo Declaration is ineffective to remove the reference of Nakazawa et al. as prior art.

Applicant argues that the reference of Nakazawa et al., does not teach all elements of the claimed embodiment of the invention. Applicant argues the Yoo Declaration II demonstrates that that Nakazawa et al., does not result in the production of a stable, clear solution. Applicant disagrees that the prior Yoo Declaration I concedes the solutions of Nakazawa as "clear", and that the Declaration plainly indicates that it is only the supernatant of Nakazawa's solution that is clear, and only after a substantial amount of precipitate has time to settle out. (See Reply entered 8/2/2005 at p. 13, para 2). Applicant argues that the compositions of Nakazawa et al. cannot be said to have been "substantially free of precipitate or particulate".

Response to Arguments

Applicant's arguments entered 8/2/2005 have been fully considered but they are not persuasive. The Yoo Declaration II is not found persuasive and does not overcome the reference of Nakazawa et al., see above Response to Declaration.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "substantially free of precipitate or particulate") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Also, applicant argues that in the compositions of Nakazawa, only the supernatants are clear, and only after substantial precipitation has time to settle out. The examiner respectfully submits that these features are not found in claims as drawn, and submits that clearness of the supernatants indicates that the solutions taught by Nakazawa are, in fact, clear.

13. Claims 138-141 are rejected under 35 U.S.C. 102(b) as being anticipated by Panini et al., Pharmacological Research, Vol. 31, No. 3/4, 1995. This rejection maintains the reasons of record as set forth in the previous Office action. The rejections are copied below for the convenience of the reader.

Panini et al., throughout the publication, and especially at the abstract, p. 205, para 6-p. 206, para 5, p. 206, and Figure 1, teach dissolution of ursodeoxycholic acid with 2-hydroxypropyl-beta-cyclodextrin, which reads upon a solution within some selected pH value, comprising bile salt, an aqueous starch conversion product, and water. Absent evidence to the contrary, aqueous solutions wherein the bile acid

and the starch conversion product are dissolved in water, will be "clear". See also rejection under 35 USC 112, second paragraph regarding the term "clear".

Applicant argues that the cited prior art does not teach all of the elements of the claimed embodiment of the invention. Applicant argues that Panini et al. fail to teach an "aqueous soluble starch conversion product" because said product, as defined in the specification at p. 22, lines 17-18, "cannot be interpreted to include cyclodextrins". Applicant states that the specification requires that if the aqueous soluble starch conversion product is polymeric, "[t]he polymer has at least one reducing end and at least one non-reducing end."

Response to Arguments

Applicant's arguments entered 8/2/2005 have been fully considered but they are not persuasive.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145. Applicant's representative does not provide objective evidence that the cyclodextrin taught by Panini, or any cyclodextrin, is not an "aqueous soluble starch conversion product".

The instant specification states:

> Based on these formulas, the aqueous solution dosage forms of various concentrations of certain bile acids (or salts) with its corresponding minimal quantity or more of high molecular weight aqueous soluble starch conversion products (for example; maltodextrin, liquid glucose, dried powder of liquid glucose (commercial corn syrup solid), dextran, dextrin,

> and soluble starch) or soluble non-starch polysaccharide (e.g. guar gum, pectin, gum arabic) were prepared.

Specification at p. 33, lines 7-12. Thus the specification teaches that dextrin is an example of an aqueous soluble starch conversion product. Therefore, a prima facie case of anticipation is made, because cyclodextrin is a dextrin. Applicant's representative does not provide objective evidence that the cyclodextrin of Panini lacks having at least one reducing end and at least one non-reducing end.

14. Claims 138-141 are rejected under 35 U.S.C. 102(b) as being anticipated by Wildauer, U.S. Patent No. 5,534,505. This rejection maintains the reasons of record as set forth in the previous Office action. The rejections are copied below for the convenience of the reader.

> Wildauer, throughout the patent, and especially at col. 2, lines 1-60, teaches ursodeoxycholic acid in demineralized water, with beta-cyclo-dextrin, at pH values between 2.5 and 8, which meet the structural elements of the claimed invention and would therefore, absent evidence to the contrary, exist as a clear aqueous solution. See also rejection under 35 USC 112, second paragraph regarding the term "clear".

Applicant argues that the cited prior art does not teach all of the elements of the claimed embodiment of the invention. Applicant argues that Wildauer fails to teach a clear aqueous solution, but instead teaches a solution in which most of the UDCA (bile acid salt) is in the form of crystalline particles.

Applicant argues that there is a chemical difference between the composition of Wildauer and the instant claims, because "[w]ithout being limited to any particular mechanism, it is believed that the solubilized UDCA in composition of the invention interacts with the solvation milieu principally through hydrogen bonding and ionic

interactions", while "the compositions of Wildauer exists as an inclusion product, bound in the hydrophobic pocket of cyclodextrin by hydrophobic interactions."

Applicant argues that the specification defines aqueous soluble starch conversion products as only those that are formed by "partial or complete hydrolysis of starch", whereas the beta-cyclodextrin of Wildauer is synthesized by bacteria in a two step process, where the first step involves the hydrolyzation of heptameric D-gluopyranose from starch, and the second, transglycosylation step process by the removal of a water molecule (dehydration). Thus "[w]ater is a product of the reaction, not a reactant."

Applicant argues that Wildauer fails to teach an "aqueous soluble starch conversion product" because said product, as defined in the specification at p. 22, lines 17-18, "cannot be interpreted to include cyclodextrins". Applicant states that the specification states that if the aqueous soluble starch conversion product is polymeric, "[t]he polymer has at least one reducing end and at least one non-reducing end."

Response to Arguments

Applicant's arguments entered 8/2/2005 have been fully considered but they are not persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a solution in which most of the bile acid salt is in the form of crystalline particles, or that the solubilized UDCA in composition of the invention interacts with the solvation milieu principally through hydrogen bonding and ionic interactions") are not recited in

the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims do not recite limitations as the amount of bile salt in solution, or as to the absence of crystalline particles, or the hydrogen bonding and ionic interactions of UDCA. Furthermore, applicant qualifies ("without being limited to any particular mechanism") the assertion that the instant claimed invention, actually has UDCA interacting with the solvation milieu principally through hydrogen bonding and ionic interactions.

In regard to the process by which the product of the invention is made as distinguishing the prior art composition, firstly the synthesis by Wildauer, teaches a hydrolyzation of heptameric D-glucopyranose from starch, even as observed by applicant. Secondly, however, the cyclodextrin is made is not relevant, because the final product being claimed, i.e., the clear aqueous solution of the claimed invention, is taught by Wildauer, even if the process of making might be different. Finally, rather than the specification requiring aqueous soluble starch conversion products as only those that are formed by "partial or complete hydrolysis of starch", (Reply at p. 15), the specification states that they may be obtained under various pH conditions from the "partial or *incomplete* hydrolysis of starch", (emphasis added, Specification at p. 22, lines 7-8).

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from

common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145. Applicant's representative does not provide objective evidence that the cyclodextrin taught by Wildauer, or any cyclodextrin, is not an "aqueous soluble starch conversion product".

The instant specification states:

> Based on these formulas, the aqueous solution dosage forms of various concentrations of certain bile acids (or salts) with its corresponding minimal quantity or more of high molecular weight aqueous soluble starch conversion products (for example; maltodextrin, liquid glucose, dried powder of liquid glucose (commercial corn syrup solid), dextran, dextrin, and soluble starch) or soluble non-starch polysaccharide (e.g. guar gum, pectin, gum arabic) were prepared.

Specification at p. 33, lines 7-12. Thus the specification teaches that dextrin is an example of an aqueous soluble starch conversion product. Therefore, a prima facie case of anticipation is made, because cyclodextrin is a dextrin. Applicant's representative does not provide objective evidence, for example, that the cyclodextrin of Wildauer does not have at least one reducing end and at least one non-reducing end.

15. Claims 138-141 are rejected under 35 U.S.C. 102(b) as being anticipated by anticipated by Ventura et al., International Journal of Pharmaceutics, vol. 149, (1997), pp. 1-13. This rejection maintains the reasons of record as set forth in the previous Office action. The rejections are copied below for the convenience of the reader.

Ventura et al, throughout the publication, and especially at p. 2, para 8, p. 7, para 2, p. 12, para 1-4 and Figure 7A and7B, teach ursodeoxycholic acid and beta-cyclo-dextrin, at pH value 1.1, dissolved in water-based solutions, which meet the structural elements of the claimed invention and would therefore, absent evidence to the contrary, exist as a clear aqueous solution. See also rejection under 35 USC 112, second paragraph regarding the term "clear".

Applicant argues that the cited prior art does not teach all of the elements of the claimed embodiment of the invention. Applicant argues that Ventura et al. fail to teach an "aqueous soluble starch conversion product" because said product, as defined in the specification at p. 22, lines 17-18, "cannot be interpreted to include cyclodextrins". Applicant states that the specification states that if the aqueous soluble starch conversion product is polymeric, "[t]he polymer has at least one reducing end and at least one non-reducing end."

Response to Arguments

Applicant's arguments entered 8/2/2005 have been fully considered but they are not persuasive.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145. Applicant's representative does not provide objective evidence that the cyclodextrin taught by Ventura et al., or any cyclodextrin, is not an "aqueous soluble starch conversion product".

The instant specification states:

> Based on these formulas, the aqueous solution dosage forms of various concentrations of certain bile acids (or salts) with its corresponding minimal quantity or more of high molecular weight aqueous soluble starch conversion products (for example; maltodextrin, liquid glucose, dried powder of liquid glucose (commercial corn syrup solid), dextran, dextrin,

and soluble starch) or soluble non-starch polysaccharide (e.g. guar gum, pectin, gum arabic) were prepared.

Specification at p. 33, lines 7-12. Thus the specification teaches that dextrin is an example of an aqueous soluble starch conversion product. Therefore, a prima facie case of anticipation is made because cyclodextrin is a dextrin. Applicant's representative does not provide objective evidence, for example, that the cyclodextrin of Ventura does not have at least one reducing end and at least one non-reducing end.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. Claims 138-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Japan Publication No. 62153220 to Nakazawa et al., Formal Translation, (IDS filed 5/17/2004) and Acharya et al., US 6,210,699. This rejection maintains the reasons of record as set forth in the previous Office action. The rejections are copied below for the convenience of the reader.

Claims 138-147 are drawn to a clear aqueous solution comprising; (i) a first material selected from the group consisting of an aqueous soluble bile acid salt, a bile acid conjugated with an amine by an amide linkage that is ursodeoxycholic acid (elected species), and combinations thereof; (ii) an aqueous soluble starch conversion product (elected species); and (iii) water, wherein the first and second materials both remain in solution for all pH values of the solution within a selected range of pH values. Claim 142 is drawn to a solution comprising one or more additional bile acids. Claims 143-147 are drawn to solution further comprising agents having anti-inflammatory activity, analgesic activity, or anticonvulsant activity, "an agent having prolonging survival time in hypoxic conditions" or an agent for alleviating or ameliorating stomatitis, gingivoglossitis or toothache. The terms, including "clear" and "an agent having prolonging survival time in hypoxic conditions" are interpreted as vague and indefinite (see the rejection of the these claims under 35 U.S.C. 112, second paragraph).

Japan Publication No. 62153220, Formal Translation, (IDS filed 5/17/2004), also known as the reference of Nakazawa et al., throughout the publication and especially at p 2, teach a clear liquid agent (p. 2, para 2, claim 1 and para 3; which reads on a clear aqueous solution) comprising ursodeoxycholic acid or chenodeoxycholic acid (p. 2, para 2, claim 2) and a dextrin that is maltodextrin, amylodextrin or erythrodextrin, (p. 2, claim 2, reading on an aqueous soluble starch conversion product (elected

species)); and (iii) water (p. 2, claim 1), wherein the first and second materials both remain in solution for all pH values of the solution within a selected range of pH values (p. 9, para 16); and at p. 2, para 2, claim 2.

The Yoo Declaration is ineffective to overcome Nakazawa et al. as a reference for the reasons provided above in paragraphs 9 of the instant Office action. Briefly, the Yoo Declaration states that solutions prepared by the method of Nakazawa et al., (called "Satoshi" in the Yoo Declaration) provide solutions that do not remain clear for a long or indefinite period of time. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., permanent clarity or transparency) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, the Yoo Declaration is ineffective to remove the reference of Nakazawa et al. as prior art.

Acharya et al., US 6,210,699, throughout the patent, including the claims, disclose a device that includes drugs, and wherein:

> The device of the present invention is also suitable for transmucosally delivery of both ionic or non-ionic drugs for oral or systemic diseases including analgesics and anti-inflammatory agents (e.g. indomethacin, ibuproden), mouth disinfectants (chlorohexidine hydrochloride, hexylresorcine), enzymes (e.g. nitroglycerin, isosorbide dinitrate, nifedipine), antiasthmatics (e.g. disodium cromoglycate), antibiotics (e.g. penicillin, erythromycin), chemotherapeutics (e.g. sulfathiazole, nitrofurazone), local anesthetics (e.g. benzocaine), cardiotonics (e.g. digitalis, digoxin), antitussives and expectorants (e.g.codeine phosphate, isoproterenol hydrochloride), agents affecting digestive organs, antihistamines, antiinflammatory steroids, hemostatics, sex hormones, sedatives, antitumor agents, or the like. Effective amounts, i.e. from 2 to 20% by weight, of penetration enhancers such as a salt of a conjugate of a bile acid with taurine or taurocholic acid may be optionally added in the active layer to enhance the penetration of the active drug.

Acharya et al., US 6,210,699, col. 8, line 59-col. 9, line 10. Thus Acharya et al. teach adding penetration enhancers, such as bile acids with taurocholic acid, which is also a bile acid, so as to add one or more additional bile acids (as in claim 142) to agents that are analgesic, anti-inflammatory, sedatives (which read on anticonvulsants), antiasthmatics (which, absent evidence to the contrary, read on "an agent having prolonging survival time in hypoxic conditions") and mouth disinfectants (which read on agents for alleviating or ameliorating stomatitis, gingivoglossitis or toothache).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have made clear aqueous solutions comprising a bile acid and a starch conversion product (as taught by Nakazawa et al.) and one or more additional bile acids, an aqueous starch derivative, water, and agents having anti-inflammatory activity, analgesic activity or anticonvulsant activity, "an agent having prolonging survival time in hypoxic conditions", or an agent for alleviating or ameliorating stomatitis, gingivoglossitis or toothache (as taught by Acharya et al.).

One of ordinary skill in the art would have been motivated to have made and used aqueous solutions comprising a bile acid and one or more additional bile acids, because Acharya teach bile acids as penetration enhancers, and teaches combining bile acid penetration enhancers with taurocholic acid, which is another bile acid, in order to facilitate delivery of the therapeutic agents. One of ordinary skill in the art would have been motivated to have made aqueous solutions comprising bile acids and starch derivatives with agents having anti-inflammatory activity, analgesic activity or anticonvulsant activity, "an agent having prolonging survival time in hypoxic conditions", or an agent for alleviating or ameliorating stomatitis, gingivoglossitis or toothache, because Acharya suggests combining such agents in bile acid containing solutions because bile acids are penetration enhancers, and because Nakazawa et al., teach combining bile acids with starch derivative to reduce the bitterness of the bile acid (Nakazawa et al, p. 3, para 03) and to produce a clear aqueous solution in which the bile acid was completely solubilized and in

which there was no bitter taste (Nakazawa et al., p. 4, para 05), in order to facilitate delivery of known therapeutic agents.

Applicant argues that the reference of Nakazawa et al., does not enable and does not teach all elements of the claimed embodiment of the invention. Applicant argues the Yoo Declaration II demonstrates that that Nakazawa et al., does not result in the production of a stable, clear solution because the compositions of Nakazawa et al. cannot be said to have been "substantially free of precipitate or particulate".

Response to Arguments

Applicant's arguments entered 8/2/2005 have been fully considered but they are not persuasive. The Yoo Declaration II is not found persuasive and does not overcome the reference of Nakazawa et al., see above Response to Declaration.

It is further noted that the claims are silent as to precipitates or particulates. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

17. Independent claim 148 is rejected under 35 U.S.C. 103(a) as being unpatentable over Japan Publication No. 62153220 to Nakazawa et al., Formal Translation, (IDS filed 5/17/2004) and Vandelli et al, International Journal of Pharmaceutics, vol. 118, (1995), pp. 77-83. This rejection maintains the reasons of record as set forth in the previous Office action. The rejections are copied below for the convenience of the reader.

Independent claim 148 is drawn to a clear aqueous solution comprising; (i) a first material selected from the group consisting of an aqueous soluble bile acid salt, a bile acid conjugated with an amine by an amide linkage that is ursodeoxycholic acid; (ii) maltodextrin; and (iii) water, wherein the first

and second materials both remain in solution for all pH values of the solution within a selected range of pH values; and wherein the weight ratio of maltodextrin to ursodeoxycholic acid is 25:1. The claim is interpreted as vague and indefinite in view of the rejection under 35 U.S.C. 112, second paragraph.

Japan Publication No. 62153220, Formal Translation, (IDS filed 5/17/2004), known as the reference of Nakazawa et al., throughout the publication and especially at p 2, teach a clear liquid agent (p. 2, para 2, claim 1 and para 3; which reads on a clear aqueous solution) comprising ursodeoxycholic acid or chenodeoxycholic acid (p. 2, para 2, claim 2) and a dextrin that is maltodextrin, amylodextrin or erythrodextrin, (p. 2, claim 2, reading on an aqueous soluble starch conversion product (elected species)); and (iii) water (p. 2, claim 1), wherein the first and second materials both remain in solution for all pH values of the solution within a selected range of pH values (p. 9, para 16); and at p. 2, para 2, claim 2, teaches a weight ratio of maltodextrin to ursodeoxycholic acid of 30:1 or higher.

The Yoo Declaration is ineffective to overcome Nakazawa et al. as a reference for the reasons provided above in paragraphs 9 of the instant Office action. Briefly, the Yoo Declaration states that solutions prepared by the method of Nakazawa et al., (called "Satoshi" in the Yoo Declaration) provide solutions that do not remain clear for a long or indefinite period of time. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., long-term clearness) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The Yoo Declaration is ineffective to remove the reference of Nakazawa et al. as prior art.

Vandelli et al., at p. 78, para 7, teach combining 1.7 g of a starch derivative, which is 2-hydroxypropyl-beta-cyclodextrin, with 487 mg of ursodeoxycholic acid (w/w ratio of 3.5:1) in a aqueous solution of a given pH.

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to have made clear aqueous solutions comprising maltodextrin to ursodeoxycholic acid in a weight ratio of 25:1.

One of ordinary skill in the art would have been motivated to have made and used aqueous solutions comprising maltodextrin to ursodeoxycholic acid in a weight ratio of 25:1 because Nakazawa et al. teach a weight ratio of maltodextrin to ursodeoxycholic acid of 30:1 and Vandelli et al. teach combining the starch derivative with ursodeoxycholic acid in a lower weight to weight ratio of 3.5:1, so that one of ordinary skill in the art would have been motivated, in routine optimization, to decrease the maltodextrin to ursodeoxycholic acid weight ratio in a range from 30:1 to 3.5:1, thus encompassing the claimed value of 25:1.

Applicant argues that the reference of Nakazawa et al., does not enable and does not teach all elements of the claimed embodiment of the invention. Applicant argues the Yoo Declaration II demonstrates that that Nakazawa et al., does not result in the production of a stable, clear solution because the compositions of Nakazawa et al. cannot be said to have been "substantially free of precipitate or particulate".

Response to Arguments

Applicant's arguments entered 8/2/2005 have been fully considered but they are not persuasive. The Yoo Declaration II is not found persuasive and does not overcome the reference of Nakazawa et al., see above Response to Declaration.

It is further noted that the claims are silent as to precipitates or particulates. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Conclusion

18. Claims 138-148 stand finally rejected.

19. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Shibuya
Examiner
Art Unit 1639

PADMASHRI PONNALURI
PRIMARY EXAMINER

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